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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,096	11/03/2000	Philip C. Wong	JHU1690-1	9634

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Lisa A Haile
Gray Cary Ware & Freidenrich LLP
4365 Executive Drive Suite 1600
San Diego, CA 92121-2189

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	7

DATE MAILED: 10/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,096	WONG ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *3 and 6-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 5* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☒ Claim(s) *1-69* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III (Claims 1, 2, 4, and 5) drawn to a method for modulating the production of Aβ11-40/42 peptide fragments *in vitro* using an anti-BACE1 antibody in Paper No. 6 (5 September 2002) is acknowledged. The traversal is on the ground(s) that the claims of Groups III, XII, XIII, XIV, and XIX are united by the common requirement of antibody administration. This is not found persuasive because Groups XII, XIII, and XIV pertain to diagnosis of Alzheimer's Disease and are separate and distinct from Group III which pertains to mechanisms of modulating Aβ11-40/42 peptide fragments *in vitro*. Groups XII, XIII, and XIV also require the extraction and analysis of biological samples from subjects, which is not required by Groups III or XIX. In addition, a nexus between the levels of Aβ11-40/42 peptide fragments *in vivo* and Alzheimer's disease must be established. Also, Group XIX is applicable to all kits containing anti-BACE1 or anti-Aβ11-40/42 antibodies whether or not they are used for diagnosis purposes. Therefore, each Group would require a separate and distinct search presenting an undue search burden on the examiner. Claims 3 and 6-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 1, 2, 4, and 5 will be examined to the extent that they read on methods of modulating the production of Aβ11-40/42 peptide fragments *in vitro* comprising contacting a sample or cell with an anti-BACE1 antibody.

Status of Application, Amendments, and/or Claims

2. Claims 3 and 6-69 are withdrawn from consideration as discussed above and claims 1, 2, 4, and 5 are under examination.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Title

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. The following title is suggested:

A METHOD OF USING AN ANTI-BACE1 ANITBODY TO INHIBIT Aβ11-40/42 PEPTIDE FRAGMENT PRODUCTION *IN VITRO*.

Specification

6. The Specification is objected to because of the following informalities: Serial Number of Provisional Application to which priority is claimed is not included on first page of specification; "Matl." is misspelled and "Southern" should be capitalized (pp. 45 line 7). Appropriate correction is required.

Claim Objections

7. Claim 5 is objected to because of the following informalities: specifically recites a non-elected invention (a BACE1 antisense molecule). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 1 is directed a method for modulating the production of Aβ11-40/42 peptide fragments comprising contacting a sample or cell containing a β-site APP-cleaving enzyme 1 (BACE1) and an amyloid precursor protein (APP) with an anti-BACE1 antibody such that production of Aβ11-40/42 is modulated. Claim 2 is directed to the modulation of Claim 1 wherein Aβ11-40/42 peptide formation is inhibited. Claim 4 is directed wherein the contacting of a sample or cell of the method of Claim 1 is *in vitro*. Claim 5 is directed to the method of Claim 1 wherein an anti-BACE1 antibody is the BACE1-modulating agent.

9. The specification teaches that the role of BACE1 in the processing of APP and fragments thereof is not well understood. The present invention provides a method for modulating (e.g. inhibiting) the interaction of a BACE1 polypeptide with its substrate APP (*in vitro*) by

administering to a cell an agent (e.g. an antibody, ribozyme, antisense molecule, or double-stranded interfering RNA molecule) that interacts with or inhibits expression of the activity of a BACE1 polypeptide. The term "agent" is used in this application can denote a chemical compound, a mixture of chemical compounds, a biological macromolecule (e.g. a peptide, peptidomimetic, or antibody), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues.

10. While general guidance is provided regarding preparing an *in vitro* system to execute the invention, no working examples are provided re: contacting a sample or cell in vitro with an anti-BACE1 antibody to inhibit the formation of Aβ11-40/42 peptides.

11. The art teaches that modulation can cover proteolytic activity (e.g. to cleave a peptide bond of a polypeptide, ability to cleave an aminoacyl bond of a polypeptide), enzyme- activity (e.g. ability to modify an enzyme in a manner that increases or decreases the enzyme's activity), protein-protein interaction (e.g. binding, formation of complexes, influencing folding or conformation) or gene transcription (e.g. ability to enhance or inhibit expression of gene, ability to enhance transcription of a gene) (Murrary et al. Harper's Biochemistry). In addition, any of the above mentioned modulators of the production of Aβ11-40/42 peptide production could be organic, inorganic, pharmaceutical, chemical, or biologically derived.

12. Thus the claimed invention is directed to an *in vitro* system for modulation of Aβ11-40/42 peptide production, which is not supported by the teachings of the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specific biological actions/activities that the compounds would effect; How does the antibody effect peptide formation; Expectation of the antibody to interfere with peptide

production. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

13. Regarding peptide formation, the art recognizes that "peptide formation" includes several steps including transcription, export of the mRNA into the cytoplasm, translation (initiation, elongation, and termination), protein folding, and post-transnational modification, and possible targeting and/or export. Due to the large quantity of experimentation necessary to evaluate all the possible effects on peptide formation, the lack of direction/guidance presented in the specification on what specific steps in peptide formation are to be acted upon, the absence of working examples directed to inhibition of peptide formation via antibodies, the complex nature of the invention, the unpredictability of the effects of antibodies (Murray et al., Harper's Biochemistry; O'Nuallain and Wetzel, 2002), and the breadth of the claims which fail to recite limitations for what effects antibodies would have on peptide formation inhibition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Regarding modulation, the art recognizes that "modulation" of transcription or activity includes a great variety of effects whether inhibiting, enhancing, or terminating. Due to the large quantity of experimentation necessary to evaluate all the possible embodiments of modulation, the lack of direction/guidance presented in the specification on what type of modulation, the absence of working examples directed to modulation, the complex nature of the invention, the unpredictability of the effects of modulation on peptide formation (Murrary et al. Harper's

Biochemistry; Lewin, Genes II), and the breadth of the claims which fail to recite limitations for what effects modulation activity would have on cells, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Finally, the application must establish a nexus between the Aβ11-40/42 peptide production recited in the claims and the inhibition via an antibody as recited in the claims. In this case, the skilled artisan is not guided as to how an antibody must affect one or more steps of the peptide production such that the antibody would be determined to be one that inhibits Aβ11-40/42 peptide production. Also, peptide production involves several steps (see discussion and references above) and it is not clear that an anti-BACE1 antibody is involved in a rate-limiting step for any of the various peptide production steps such that it could be used to inhibit Aβ11-40/42 peptide production.

16. Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The method steps do not indicate how the anti-BACE1 antibody must affect Aβ11-40/42 peptide production in order for the anti-BACE1 antibody to be labeled a "modulator" as recited in preambles. Thus the claims are incomplete.

Summary

17. Claims 1, 2, 4, and 5 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmer

CJN
October 3rd, 2002

ELIZABETH [illegible]
PRIMARY EXA[illegible]